REMARKS

Claims 57-115 are pending in the Application. Applicants elected Group 1, Claims 57-83 in a Reply to Restriction Requirement, dated July 26, 2003. Claims 84-115 are drawn to a non-elected invention. Applicants reserve the right to file a continuing application or take such other appropriate action as deemed necessary to protect the non-elected inventions. Applicants do not hereby abandon or waive any rights in the non-elected inventions. Applicants note that the Office Action states Claims 53-115 are pending in the Application, clarification is respectfully requested with respect to Claims 53-56.

Claim 57 has been amended. Support for this amendment is found in the Specification on page 3, lines 16-20. Claims 59, 60, 73 and 74 have been amended. Support for this amendment is found in the Specification on pages 16, line 26 to page 17, line 2. No new matter is added.

Objection to the Title of the Invention

The title of the invention is objected to as not descriptive because the instant title is directed to inhibitors while the claimed subject matter is directed to a method.

The title has been amended to refer to a method; thus, as amended, the title clearly describes the claimed subject matter.

Rejection of Claims 59, 60, 73 and 74 under 35 U.S.C. § 112, Second Paragraph

Claims 59, 60, 73 and 74 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that in Claims 59, line 9; 60, line 3; 73, line 9; and 74, line 3, the phrase "improved inhibition" causes the claims to be vague and indefinite because it is unclear as to what is being used to consider the inhibition of a molecular interaction has been improved (reduction in interaction between ligand and target protein, or change in target protein conformation).

Applicants have replace the word "improved" with "increased" in referring to inhibition of macromolecular ligand/target protein binding compared with analog. As amended the claims

are now clear and definite. Reconsideration and withdrawal of the rejections is respectfully requested.

Rejection of Claims 57-83 under 35 U.S.C. § 112, First Paragraph

Claims 57-83 are rejected under 35 U.S.C. § 112, first paragraph, because the Examiner states that the specification while being enabling for an interleukin-2 receptor (page 9, lines 24-29) and MCP1 (page 12, line 22 to page 15, line 11), does not reasonably provide enablement for any macromolecular ligand and target protein complex. The Examiner further details that the method relies on data derived from an unpredictable art such as protein crystallization and thus would require clear and precise guidance for one skilled in the art to reliably use the said method. Applicants respectfully disagree.

Applicants disclose methods of identifying a compound that covalently binds to the surface of a target protein in sufficient proximity to the binding site between a macromolecular ligand and the target protein to inhibit binding of the macromolecular ligand with the target protein. In one embodiment, the complex between the target protein and macromolecular ligand is modeled computationally, by x-ray crystallography, by nuclear magnetic resonance spectrophotometry or by active site localization; the target protein/macromolecular ligand binding site is identified from the model(s); and a lead compound is designed based on its ability to bind to the protein target/macromolecular ligand binding site.

The Examiner has erroneously implied that x-ray crystallography is a subset of a computational model. See Office action, page 4, item 12. These methods are not a genus/species, but two different models. As detailed in the Specification on page 11, lines 2-7, "[m]ethods of preparing such models are well known in the art and include computational models, x-ray crystal structures, structures obtained from nuclear magnetic resonance data and methods of binding site localization such as site directed mutagenesis." Four different models are disclosed for utilization in modeling. X-ray crystal structures are not a subset of a computational model. This distinction is important because the methods are not limited by protein crystallization. In instances where crystals are not available, NMR techniques are widely used (Erickson and Fesik, *Annual Reports in Medicinal Chemistry*, **1992**, *27*, 271, see page 279,

Exhibit A). X-ray crystallography and NMR are complementary techniques (*Ibid.*, Erickson and Fesik, see page 285).

Further, a computational approach can be used to generate structural models. For example, if the crystal structure of one family member of a class of proteins is known then this known information can be substituted for another related member of the family. Therefore, when there is significant sequence similarity (above 50%) in a particular family of proteins, comparative modeling (using known structures as templates) can be employed. In fact, up to 90% of the polypeptide conformation tend to be well modeled when the family members have 30%-50% identity. On the other hand, if there is insignificant sequence similarity among the members (below 30%) then other structural features, such as fold recognition (*i.e.,* is the sequence compatible with a known fold) can be employed (Baker *et al., Applied Bioinformatics*, 2003, *2-Suppl 3*, S3, **Exhibit B** and Zhang and DeLisi, Cellular and Molecular Life Sciences, 2001, *58*, 72, **Exhibit C**).

The Examiner further states that "In essence, protein crystallization is still a trial and error process because the current technology for producing protein for the crystallization process is unpredictable, which results in high failure rate for proteins that are being crystallized. Therefore, researches continue to have trouble generating sufficient protein for the crystallization process (New Focus, Science, 2002)."

A complete review of the article indicates that the author's focus is on the subsequent outcome of the Human Genome Project, specifically that structural biologists intend to map all of the human proteins. The approach detailed in this article is different from the accepted drug discovery approach. In traditional drug discovery, the structure of proteins **with** biological interest are determined.

This difference is exemplified in the article. "But the new strategy is a departure from tradition. The ability to sequence full genomes 'has turned structural biology on its head,' "says Chris Sander, a computational biologist at the Memorial Sloan-Kettering Cancer Center in New York City. Instead of choosing targets because they are biologically interesting, structural genomics researchers can now scan genomic databases for stretches of DNA encoding genes of completely unknown function, hunt down their proteins, study the results, and perhaps discover entirely new realms of biology in the process." See New Focus, Science, 2002 article (page 949,

paragraph 2):

The 'trial and error process' referred to in the passage is because the structural genomics researches are working on **unknown** protein targets. When working with a known protein family, such as, the interleukins, described in the instant application, similar expression, purification, and crystallization techniques can be employed for all interleukin members including newly discovered members of this biologically important family. The efficiency of this process is evidenced by the rapid growth of x-ray structures deposited in the Protein Data Bank (55 separate listing under Interleukin, see **Exhibit D**). When the structure is likely to be known or crystallization techniques used for a particular protein, one can likely use this data for a related protein of interest from the same protein class.

In stark contrast to the Examiner's assertion, the automation of x-ray crystallography has undergone significant advancements (Abola *et al., Nature Structural Biology, Structural Genomics Supplement*, **2000**, 973, **Exhibit E**), and is routinely applied to the drug discovery process (Blundell *et al*, Nature Reviews, Drug Discovery, 2002, *1*, 45, **Exhibit F**).

The instant application defines specific protein targets with biological activity and pharmaceutical relevance. Protein crystallization, is neither a required element in the claims nor a prerequisite to practice the method. If protein crystallization data is known, then this data may be used for designing a targeting group, however, other methods and data can also be utilized to accomplish this same purpose.

In view of the cited art and extensive guidance, including specific examples, (IL-2 and MCP-1) provided in the Specification, the person of ordinary skill in the art could make and use the claimed methods without undue experimentation. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 57-63, 65-67, 70-77, 79-81 and 83 under 35 U.S.C. § 102(b)

Claims 57-63, 65-67, 70-77, 79-81 and 83 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Ladner *et al.* (US 5,223,409 A). Applicants respectfully disagree.

Ladner *et al.* describes an invention where a DNA sequence is used to foster the biosynthesis of novel mini-proteins having desired binding characteristics. The mini-peptide sequence is then recovered by affinity chromatography and subsequent analyses provides a

peptide sequence. The focus of their invention is the biosynthesis of peptides from DNA codons, and the associated methods of these techniques. Ladner *et al.* utilizes biological phage particles in this process.

Claim 57 is an assay for identifying potent inhibitors of binding between a target protein and a macromolecular ligand of the target protein. The method is applicable to a large number of target proteins. Assays for identifying compounds that inhibit protein/macromolecule binding are disclosed.

Applicant's claimed assay requires step c) in which a target protein is combined with a macromolecular ligand and each analog under conditions suitable for covalent binding between the target protein and macromolecular ligand. The claimed assay additionally requires a step d) whereby each combination of step c) is assayed for inhibition of macromolecular ligand/target protein binding and for covalent binding between the analog and the target protein. The compounds identified covalently bind to the surface of a target protein in sufficient proximity to the binding site between a macromolecular ligand and the target protein to **inhibit** binding of the macromolecular ligand with the target protein.

Ladner *et al.* does not describe covalent binding or methods for obtaining inhibitory compounds. Ladner *et al.* also does not describe the step of assessing the inhibition such as described in step c) and d) of Applicants' claimed subject matter. Therefore, Ladner *et al.* does not meet the limitations of step c or d. The Ladner *et al.* patent merely describes directed evolution of novel binding proteins, utilizing mutagenesis, expression, chromatographic selection and amplifications. The conditions and steps described in Applicants' claimed invention are not disclosed in the Ladner *et al.* patent.

The Examiner is respectfully requested to identify the portion of Ladner *et al.* that describe these steps. Absent this specific teaching, the cited reference fails to anticipate Applicants' claimed assay. Reconsideration and withdrawal of the rejection are respectfully requested.

Information Disclosure Statement

The Information Disclosure Statements (IDS) were filed on September 25, 2002 and October 1, 2002 are deemed as failing to comply with 37 C.F.R. § 1.98(a)(2), which requires a

legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Applicants have enclosed copies of the postcards showing the references were in fact received in the patent office. Thus, Applicants do not believe additional fees are needed for these Information Disclosure Statements.

To assist the Examiner, additional copies of the references cited in these IDS' are enclosed herein. Applicants request the Examiner consider the references and initial the PTO 1449 forms. Additionally, a Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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Dated: March 30, 2004